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## (54) Anti-aging compositions for cosmetic use

(57) Compositions comprise a combination of an anti-elastase agent, an anti-collagenase agent and an agent that stimulates collagen III synthesis in an cosmetic excipient.

Anti elastase agents may be tannin, oleic acid, uvaol or  $\alpha$ -2 macroglobulin. The anti collagenases may be EDTA, L-cysteine, metal ions or mercaptans. Collagen III synthesis stimulators may be a fatty acid ester of ascorbic acid or hydroxyproline etc.

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COSMETIC COMPOSITION AND BEAUTY TREATMENT  
METHOD COUNTERACTING SKIN AGEING

The present invention relates to a cosmetic composition comprising an effective amount of a combination of three types of substances displaying different activities.

5 The present invention also relates to a beauty treatment method counteracting skin aging.

In order to alleviate the phenomenon of skin aging, cosmetology has developed various cosmetic compositions.

10 These compositions can contain nutrients for the cells (amino acids, sugars, vitamins, etc), constituent components of the skin (collagen, elastin, essential fatty acids, factors, NMF, etc) and agents affording protection against the external environment (free-radical  
15 scavengers, film-forming agents, anti-UVA screening agents, etc).

20 Since the activity of these different cosmetic compositions is relatively short-lived and only slightly effective, it hence proved useful to develop cosmetic compositions displaying lasting and effective activity.

25 The authors of the present invention discovered, surprisingly, that the combination of an effective amount of three types of known substances had a synergistic activity for counteracting skin aging, in comparison with the activity of the substances taken separately.

30 Thus, the present invention relates to a cosmetic composition, characterized in that it comprises an effective amount of a combination of an anti-elastase agent, an anti-collagenase agent and an agent that stimulates collagen III synthesis, in a suitable cosmetic excipient.

35 As an agent that stimulates collagen synthesis, it is possible to use the products described in Patent Application EP-0,537,092 and in Patent Application FR 93/05,050. These products comprise, as an agent that stimulates collagen III synthesis, fatty esters of ascorbic acid, and in particular its palmitate, the palmitate of collagen hydrolysate and the fatty esters of hydroxyamino acids such as hydroxyproline, and more

especially its palmitate.

These agents are contained in vesicular carriers which can be liposomes obtained, for example, according to the process described in FR-A-2,649,335 or nanospheres.

Vesicles comprising phospholipids and hydroxyproline palmitate in combination with cholesterol are especially preferred.

The single-membrane phospholipid structure of these "carriers" is rhombohedral. They thus afford a surface/volume ratio greater than that of spherical carriers.

This composition is described as having a stimulatory activity that triggers a non-dose-dependent response by fibroblasts, arousing in them their capacity to synthesize collagen III.

This stimulatory activity is due to the rhombohedral structure and to the mixture of the three substances in an effective amount. Thus, in carriers of phospholipid type, the phospholipids (lecithin) represent 70 to 95% by weight on a dry basis, cholesterol represents 1 to 15% by weight on a dry basis and the amino acid/alcohol dipalmitate 1 to 15% by weight on a dry basis of the composition.

This composition counteracts the phenomenon of skin aging.

As regards the preparation of the composition that stimulates collagen III synthesis, it is necessary to work in a sterile medium with equipment which is also sterilized. The active principles, in well-defined proportions, are mixed according to a precise order.

The anti-collagenase agent can be a chelating agent such as EDTA, L-cysteine, metals such as  $Fe^{++}$ ,  $Cu^{++}$  and  $Zn^{++}$  and mercaptans, it being possible for the anti-collagenases to be of natural origin, plant origin and serum origin ( $\beta_1$ -anti-collagenase,  $\alpha_2$ -macroglobulin). Reference may be made in this connection to "Handbook of Enzyme Inhibitors", 2nd Edition, A and B by Helmward Zollner, pp. 131 to 135.

The anti-elastase agent may be chosen from anti-elastases of plant origin such as tannin, oleic acid, the triterpene uvaol and cucurbita maxima; anti-elastases of fungal origin such as cephalosporin; anti-elastases of serum origin such as  $\alpha$ -macroglobulin; and anti-elastases of natural origin, and the like (propionylamino acid derivatives, thiazolidinecarboxylic acid derivatives). Reference may be made in this connection to "Handbook of Enzyme Inhibitors", 2nd Edition, A and B by Helmward 10 Zollner, pp. 195 to 199).

Preferably, the combination of the anti-elastase and anti-collagenase agents and the agent that stimulates collagen III synthesis represents 0.3 to 10% by weight of the composition, and the different agents are present in 15 the proportion of 0.1 to 5% by weight of the composition.

The appropriate cosmetic excipients are, of course, chosen according to whether the compositions are in the form of a cream, a fluid emulsion or a gel.

The activity of the cosmetic compositions of the 20 present invention was tested in comparison with that of compositions comprising the three agents separately.

The tests consist in examining the pattern of micro-depressions (PmD) of the skin by computer-aided vision (CAV) and measuring the depth of the wrinkle, as 25 well as measuring skin firmness.

The objective of the evaluation of the structural components of the micro-contours of the skin is to evaluate in man the effect of a cosmetic or body hygiene product on the structural components of the micro-contours of the skin, using a quantification by CAV. 30

The tests are carried out on healthy volunteer subjects, informed beforehand of the nature of the experiment and who have given their informed consent.

Precision impression of the skin:

35 - XANTOPREN® VL (BAYER), low viscosity material based on silicone crosslinking by condensation.  
- OPTOSIL® - XANTOPREN® ACTIVATOR (BAYER), liquid activator.  
- Farbkonzentrat BLAU RL, blue dye.

Image analyser:

This comprises:

- An IVC 800 BC video camera (SONY) equipped with an MD MACRO 50 mm 1:3.5 objective; Ø = 55 mm (MINOLTA)
- 5 and connected to a monitor (SONY);
  - An IBM PC compatible microcomputer;
  - An image analysis techniques training software package, MICROMORPH (Centre de Morphologie Mathématique de l'Ecole des Mines de Paris [Mathematical Morphology 10 Centre of Paris School of Mines]).

Equipment:

- Binocular magnifier (NIKON).

The method is as follows:

The exploration area varies in accordance with 15 the indication for which the product is tested. Anatomical landmarks are chosen in order to define the area carefully. In the present case, the skin of the face is the region which will be tested.

The impression mixture is prepared at the time of 20 use: 2.5 grams of XANTOPREN® VL and 45 milligrams of Farbkonzentrat BLAU RL are mixed with 3 drops of OPTOSIL®

- XANTOPREN® ACTIVATOR for 30 seconds.

Impression-taking is performed before treatment 25 on unwashed skin which has not received any product for at least 8 hours.

Subjects are settled comfortably, and the plane of inclination of the head is determined. Using a spatula, the impression mixture is rapidly applied in a uniform layer to the exploration area. The surface 30 covered is approximately 25 to 30 cm<sup>2</sup>. The setting time in order to permit polymerization is approximately 2 minutes. Detachment of the impression takes place from the upper edge, in the direction of the hairs and the down.

35 Impression-taking on treated skin is done as an immediate effect, either 15 minutes after application of the product and/or after a frequency and a time of application which are defined by the instigator of the experiment.

Impressions are examined using a binocular magnifier at a magnification of 15 and/or 20. A carefully identified area is stored in the computer memory and quantification of the different structural components of the micro-contours of the skin, pattern of surface micro-depressions (PmD) and polygons, is done by computer-aided vision.

5 The results of the effect of the products tested on the changes in the structural components of the micro-contours of the skin are expressed by:

10 - The differences between the integrals of the structural components of the micro-contours of the skin, pattern of surface micro-depressions (PmD) and polygons, before and after treatment.

15 The changes are calculated according to the formula:

$$\frac{\text{Integral after treatment} - \text{Integral before treatment}}{\text{Integral before treatment}} \times 100$$

20 - Clinical appraisal of the structural components of the micro-contours of the skin observed with the binocular magnifier before and after treatment.

25 The measurement of skin firmness has as its principle suction of the epidermis with a probe under a constant partial vacuum which is adjustable from 0 to 500 mbar depending on the areas to be studied.

The movement of the epidermis in the probe is measured by two optical lenses.

30 The rise of the epidermis corresponds to the extensibility, its fall to the tonicity.

The ratio of the tonicity  
extensibility

35 measurements is calculated by computer and evaluates the firmness, between 0 and 1.

The equipment comprises:

- 1 SEM 474 firmness gauge
- 1 AMSTRAD 1640 SD computer
- 1 PANASONIC KX P1124 printer

The protocol consists in performing, after adjusting the partial vacuum in mbar and the time of rise and release of the epidermis in the probe, a series of three measurements on a particular area 5 before and after treatment, under identical conditions.

The two tests described above gave results which show that the combination of an effective amount of the anti-elastase and anti-collagenase agents and the agent that stimulates collagen III synthesis has a 10 synergistic effect for counteracting skin aging, compared to the effect obtained under the same conditions with the three agents tested separately.

The subject of the present invention is also a beauty treatment method counteracting skin aging, 15 characterized in that an effective amount of a cosmetic composition according to the present invention is applied to the skin.

In the different formulations which follow, the expression "firmness complex" means "combination of the 20 three types of substances according to the invention", that is to say from 0.1 to 5% of each of the agents, namely an anti-elastase agent, an anti-collagenase agent and an agent that stimulates collagen III synthesis.

Examples of typical cosmetic compositions are 25 the following:

EXAMPLE 1

Care Cream

	Demineralized water	qs		
	C <sub>8</sub> /C <sub>10</sub> Triglyceride	1	to	10 %
30	Glyceryl trilauroate	1	to	5 %
	Silicone	1	to	8 %
	Glucate SS®	1	to	15 %
	Stearic acid	1	to	10 %
	Cetyl alcohol	1	to	8 %
35	Polyacrylic acid	1	to	5 %
	Triethanolamine	0.1	to	1 %
	Preservatives	0.3	to	1 %
	Firmness complex	0.3	to	10 %

EXAMPLE 2

Fluid Emulsion

	Demineralized water	q.s	
	Propylene glycol	1	to 3 %
5	Glycerol	1	to 8 %
	PCA	0.05	to 1 %
	L-Lysine	0.2	to 1 %
	Na <sub>4</sub> EDTA	0.01	to 0.1 %
	Carbopol 941®	0.1	to 2 %
10	Stearoxydimethicone	0.5	to 3 %
	Ethylhexyl cocoate	5	to 8 %
	Mineral oil	1	to 15 %
	Arlacel 60®	1	to 8 %
	Brij 58®	0.1	to 1 %
15	Preservatives	0.3	to 1 %
	Firmness complex	0.3	to 10 %

EXAMPLE 3

Gel

	Demineralized water	q.s.p	
20	Glycerol	5	to 20 %
	Na <sub>4</sub> EDTA	0.01	to 0.5 %
	Sepigel 305®		
	Preservatives	0.3	to 1 %
	Firmness complex	0.3	to 10 %

25       Example of preparation of the fluid emulsion:  
A gel is prepared by introducing Carbopol 941 powder (0.1 to 2% by weight) with vigorous agitation into cold water, which is vortexed.

30       Separately, an aqueous phase is prepared by mixing the components propylene glycol (1 to 3% by weight), glycerol (1 to 8%), PCA (0.05 to 1%), L-lysine (0.2 to 1%), Na<sub>4</sub> EDTA (0.01 to 0.1%) and preservatives (0.3 to 1%). The abovementioned mixture is then heated to 70-75°C with agitation and the gel prepared above is thereafter introduced into the aqueous phase.

35       The fatty phase is prepared by heating the

collective constituents stearoxydimethicone (0.5 to 3%), ethylhexyl cocoate (5 to 8%), mineral oil (1 to 15%), Arlacel 60 (1 to 8%) and Brij 58 (0.1 to 1%) to 75-80°C. The fatty phase is then drawn into the aqueous 5 phase with the gel. A vacuum is applied. The mixture is allowed to cool to 35°C in order to introduce the "firmness complex" (0.3 to 10% by weight). The mixture is agitated and allowed to cool under vacuum. At 25°C, the agitation is stopped and the preparation is 10 checked.

CLAIMS

1. Cosmetic composition, comprising an effective amount of a combination of an anti-elastase agent, an anti-collagenase agent and an agent that stimulates collagen III synthesis, in a suitable cosmetic excipient.
- 5 2. Cosmetic composition according to Claim 1, in which the combination of an anti-elastase agent, an anti-collagenase agent and an agent that stimulates collagen III synthesis represents 0.3 to 10% by weight of the composition.
- 10 3. Cosmetic composition according to Claims 1 and 2, in which the anti-elastase agent is present in the proportion of 0.1 to 5% by weight of the composition.
- 15 4. Cosmetic composition according to Claims 1 and 2, in which the anti-collagenase agent is present in the proportion of 0.1 to 5% by weight of the composition.
- 20 5. Cosmetic composition according to Claims 1 and 2, in which the agent that stimulates collagen III synthesis is present in the proportion of 0.1 to 5% by weight of the composition.
- 25 6. Cosmetic composition according to any one of the preceding claims, in the form of a cream, a fluid emulsion or a gel.
- 30 7. Beauty treatment method counteracting skin aging, in which an effective amount of a cosmetic composition according to Claims 1 to 6 is applied to the skin.
8. A cosmetic composition substantially as hereinbefore described with reference to Examples 1 to 3.

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**Patents Act 1977**  
**Examiner's report to the Comptroller under Section 17**  
**(The search report)**

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<b>Relevant Technical Fields</b>	Search Examiner M R WENDT
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(ii) Int Cl (Ed.6)      A61K 7/00, 7/48	Documents considered relevant following a search in respect of Claims :- 1 TO 8

**Categories of documents**

X: Document indicating lack of novelty or of inventive step.	P: Document published on or after the declared priority date but before the filing date of the present application.
Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.	E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.
A: Document indicating technological background and/or state of the art.	&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
A	WPI Accession No. 93-260440/33 & FR 2683720 A1 (JOUVANCE) see Abstract	1, 6

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